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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/320,156	05/26/99	ROSENBLUM M	D5425CIP2

HM22/0426

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EXAMINER	
CANELLA,K	
ART UNIT	**PAPER NUMBER**
1642	8

DATE MAILED: 04/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/320,156	Applicant(s) Rosenblum
	Examiner Karen Canella	Group Art Unit 1642

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire _____ month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-21* is/are pending in the application.

Of the above, claim(s) *1-14, 20, and 21* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *15-19* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election with traverse of Invention II in Paper No. 7 is acknowledged. The traversal is on the ground(s) that there is a unity of invention between Inventions I, II, III and IV. Applicant submits that the products of Inventions I and II represent the same immunoglobin linked to variant toxins, gelonin and TNF. Likewise, the applicant believes that the methods of Inventions III and IV cannot be carried out without the products of Inventions I and II. This is not found persuasive because the toxins gelonin and TNF of Inventions I and II respectively, not only are obtained from widely differing natural sources but have widely differing mechanisms of action. TNF is the ligand for TNF receptor. Activation of the TNF receptor activates a variety of intracellular signal transduction cascades and can result in the apoptotic death of the cell. Gelonin is a ribosomal-inactivating protein which inhibits protein synthesis in mamallian cells, but is inactive extracellularly. The antibody carrying the gelonin conjugate or fusion would have to be internalized to result in cytotoxicity. The antibody carrying the TNF can deliver the ligand to the TNF receptor without being internalized by the cell. Thus, the variant toxins carried by the same antibody can impart a widely differing properties to Inventions I and II. Therefore the searches for Inventions I-IV would not extensively overlap.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-21 are pending.

Claims 1-14 and 20-21, drawn to non-elected inventions, are withdrawn from examination.

Claims 15-19 are examined on the merits

3. Claim 19 was inadvertently left out of the grouping set forth in the Restriction Requirement. It is placed in Group II and will be examined on the merits.

Drawings

4. The drawings are objected to because of the reasons set forth on the enclosed PTO-948. Correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 16-18 recite the limitation "said single chain antibody". There is insufficient antecedent basis for this limitation in the claim.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 18 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 18 is rejected under 35 USC 112, first paragraph as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete

evidence either that the claimed biological materials are know and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the cell line producing scFv-23. It is not clear that single chain antibodies possessing the identical properties of scFv-23 are known and are publicly available or can be reproducibly isolated from nature without undue experimentation. For example, Mehta and Cheema (Leukemia and Lymphoma, 1999, 32 (5-6), pp 441-449), state on page 443: "the ligation of cell-suface CD38 with agonistic monoclonal antibodies...has been shown to trigger a number of responses including proliferation of mature B lymphocytes and myeloid leukemia cells, rescue from apoptosis of geminal centers and growth-suppression of stroma-supported cultures of B-cell progenitors". Thus, it can be concluded that differing monoclonal antibodies to CD38 could produce widely differing effects in vivo, some of which would notbe consistent with the particular method of treating an individual having a pathophysiological state by administering an undefined monoclonal antibody to CD38.

Exact replication of a cell line is an unpredicatable event. Although the applicant has provided a written description of a method for recombinantly constructing a single chain antibody directed against the extracellular epitope of c-erbB-2, this method will not necessarily reproduce single chain antibodies and cell lines which are chemically and structurally idenical to those claimed. It is unclear that one of skill in the art could derive single chain antibodies and cell lines identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and cell line species to obtained the claimed antibodies and cell line.

Because one of ordinary skill in the art could not be assured of the availablity to practice the invention as claimed in the absence of the availability of the claimed single chain antibody, scFv-23, a suitable deposit of the cell line producing scFv-23 for patent purposes, evidence of public availability of cell lines producing scFv-23, or evidence of reproducibility without undue experimentation of the claimed single chain antibodies is required.

If the scFv-23 producing cell line deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposit of the scFv-23 producing cell line have been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit of the scFv-23 producing cell line will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is neccessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit of the scFv-23 producing cell line are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CRF 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his/her signature and registration number averring:

(a) during the pendancy of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of the deposit or for the enforcable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced should they become non-viable or non-replicable.

Ammendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited cell line is producing the single chain antibodies scFv-23 as described in the specification as filed and are the same as those deposited in the depository, stating that the deposited cell line is producing identical single chain antibody scFv-23 described in the specification and were in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 15 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenblum (Cancer Communications, 1991) in view of Hudziak (Molecular and Cellular Biology, 1989). Claim 15 and 19 are drawn to a composition comprising a conjugate of tumor necrosis factor to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein.

Rosenblum discloses the conjugate of tumor necrosis factor to an antibody which binds specifically to epitope A of gp240 antigen found on the surface of melanoma cell lines and fesh tumor samples. Rosenblum does not teach the conjugate of tumor necrosis factor to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein. Hudziak teaches an anti-$p185^{HER2}$ /anti-c-erbB-2 monoclonal antibody which increases the sensistivity of $p185^{HER2}$ expressing tumor cells to the cytotoxic effects of TNF.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to conjugate TNF to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein. Hudziak has demonstrated that cells expressing HER2/c-erbB-2 showed increased resistance to the cyctotoxic effects of TNF and that this resistance can be overcome by the co-administration of an anti-proliferative antibody directed against the extracellular portion of the c-erbB-2 protein. Rosenblum discloses an improvement of cytotoxicity, reduction of cellular resistance, and improved tumor-targeting of TNF in human melanoma cell lines by the use of a conjugate of tumor necrosis factor to an antibody which binds specifically to an extracellular portion of gp240 protein which is expressed on human melanoma cell lines.

One of ordinary skill in the art would have been motivated to conjugate TNF with an antibody directed against the extracellular epitope of c-erbB-2 protein with a reasonable expectation of success by the teachings of Rosenblum in view of Hudziak. One of skill in the art would have been motivated to conjugate TNF with an antibody directed against the extracellular epitope of c-erbB-2 protein to attain an antiproliferative and heightened cytotoxic effect as taught by Hudziak and an improvement in the tumor-targeted delivery of TNF as taught by Rosenblum.

11. Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenblum (Cancer Communications, 1991) and Hudziak (Molecular and Cellular Biology, 1989) as applied to claim 15 and 19 above, and further in view of Bird (1988). Claims 16 and 17

are drawn to a recombinant fusion protein between a single chain antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2, and tumor necrosis factor. Bird teaches methods of making and and advantages of using recombinant single chain fusion antibodies.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to fuse TNF to an single chain antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein. Rosenblum in view of Hudziak revealed the utility of administering TNF conjugated to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein to increase the cyctotoxic effects of TNF while imparting the anti-proliferative effect of the antibody binding to the extracellular c-erbB-2 protein. Bird teaches the recombinant construction of single chained antibodies and their inherent advantages over monoclonal antibodies in the therapy of cancers.

One of ordinary skill in the art would have been motivated to fuse TNF with a single chain antibody directed against the extracellular epitope of c-erbB-2 protein with a reasonable expectation of success by the teachings of Rosenblum in view of Hudziak and in further view of Bird. One of skill in the art would have been motivated to fuse TNF with a single chain antibody directed against the extracellular epitope of c-erbB-2 protein to attain an antiproliferative and heightened cytotoxic effect as taught by Hudziak, an improvement in the tumor-targeted delivery of TNF as taught by Rosenblum, in addition to the convenience of recombinant expression, the faster in vivo clearing rate, and the enhanced ability of the smaller single chain molecule to penetrate the microcirculation surrounding solid tumors as taught by Bird.

12. Claim 18 is free of the art.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

NANCY A. JOHNSON, PH.D
PRIMARY EXAMINER

Karen A. Canella, Ph.D. KAC

Patent Examiner, Group 1642

April 19, 2000